Final Report

3-Month Intranasal Study with Metoclopramide Nasal Spray in Rabbits with a 1-Month Recovery

PREPARED FOR:
Roberts Pharmaceutical Corporation

COVANCE STUDY NUMBER:
6988-102

COVANCE.
THE DEVELOPMENT SERVICES COMPANY

Sponsor:

Roberts Pharmaceutical Corporation
Eatontown, New Jersey

FINAL REPORT

Study Title:

3-Month Intranasal Study with Metoclopramide Nasal Spray in Rabbits with a 1-Month Recovery

Author:

Lisa B. Biegel, PhD

Study Completion Date:

Testing Facility:

Covance Laboratories Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704-2595

Laboratory Study Identification:

Covance 6988-102

QUALITY ASSURANCE STATEMENT

This report has been reviewed by the Quality Assurance Unit of Covance Laboratories Inc., in accordance with the Food and Drug Administration (FDA) Good Laboratory Practice Regulations, 21 CFR 58. The following inspections were conducted and findings reported to the study director and study director management. Written status reports of inspections and findings are issued to Covance management according to standard operating procedures.

Inspection Dates		Phase	Date Reported to Study Director and Study Director Management
From	To		
		Protocol Review	
		Postlife	
		Data Review	
		Protocol Amendment Review	
		Data Review	
		Protocol Amendment Review	
		Report Review	
		Data Review	
		Report Review	
		Data Review	
		Report Review	
		Report Review	

Representative
Quality Assurance Unit

Date

STUDY IDENTIFICATION

3-Month Intranasal Study with Metoclopramide Nasal Spray in Rabbits with a 1-Month Recovery

Test Material	Metoclopramide Nasal Spray
Sponsor	Roberts Pharmaceutical Corporation 4 Industrial Way West Eatontown, New Jersey 07724-2274
Study Monitor	Diann Blanset, MS Roberts Pharmaceutical Corporation 732.676.1330
Study Location	Covance Laboratories Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704-2595
Study Director	Lisa B. Biegel, PhD Covance Laboratories Inc. PO Box 7545 Madison, Wisconsin 53707-7545 608.245.7093
Study Timetable	
Study Initiation Date	
In-Life Start Date	
In-Life End Date	
Study Completion Date	

KEY PERSONNEL

3-Month Intranasal Study with Metoclopramide Nasal Spray in Rabbits with a 1-Month Recovery

Study Director	Lisa B. Biegel, PhD
Study Toxicologist	Dennis J. Hensen, BS, LAT
Study Coordinator	Beth A. Wunderlin, BS, MT (ASCP)
Supervisor, Small Animal Toxicology	Shelley A. Dyreson, AAS, LAT
Supervisor, Dose Formulation	Dixie Bushee, BS, LATG
Associate Director, Laboratory Animal Medicine	Donna J. Clemons, DVM, MS Diplomate, ACLAM
Clinical Pathologist	Robert L. Hall, DVM, PhD Diplomate, ACVP (Clinical Pathology)
Supervisor, Clinical Pathology	Ronald Markevitch, BS, MT (ASCP)
Anatomic Pathologist	Thomas E. Palmer, PhD
Supervisor, Anatomic Pathology	Laurie J. Schuller, BA, LAT
Supervisor, Anatomic Pathology	Kimberly W. Durland, BS, HT
Director, Metabolic Chemistry	Philip J. Teitelbaum, PhD
Pharmacokineticist, Metabolic Chemistry	Magdy H. AbdelHameed, PhD
Principal Analytical Investigator, Bioanalytical Chemistry	Glenn D. Hanson, MS
Supervisor, Bioanalytical Chemistry	Lonnie J. Schultz

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ABSTRACT

The purpose of this study was to assess the toxicity and to determine the bioavailability of Metoclopramide Nasal Spray when administered as an intranasal spray to rabbits for at least 13 weeks and to assess the reversibility of any effects after a 4-week recovery period.

Male and female Hra:(NZW)SPF rabbits were assigned to four groups (eight animals/sex in Groups 1 and 4 and four animals/sex in Groups 2 and 3). The animals received dose preparations containing the control material (0.9% Sodium Chloride for Injection, USP) or 80, 160, or 240 mg of metoclopramide/animal/day; the control or test material was administered four times/day at approximate 2-hour intervals. Four animals/sex in Groups 1 and 4 were designated as recovery animals and underwent 4 weeks of recovery following 13 weeks of dose administration.

Food was provided at approximately 150 g/day. Water was provided *ad libitum*. The animals were observed twice daily (a.m. and p.m.) for mortality and moribundity. Once daily, each animal was observed cageside for abnormalities. Once weekly, each animal was removed from its cage and examined for abnormalities and signs of toxicity. Ophthalmic examinations were done on all animals before initiation of treatment and during Week 13. Nasal irritation was evaluated and scored before animal assignment to study, on Day 1, weekly thereafter during treatment and recovery, and on the day of necropsy. Individual body weights were recorded once prior to treatment, on the first day of treatment, and weekly thereafter. Food consumption was confirmed qualitatively by daily visual inspection. Blood samples were collected for bioavailability analysis from each animal once prior to the first dose administration of the day and at approximately 10, 20, 30, 60, and 120 minutes after the last (fourth) dose administration on Days 1, 30, and 92. Blood samples collected from the control animals (Group 1) were discarded without being analyzed. All other plasma samples were harvested and stored in a freezer, set to maintain -10 to -30°C, until analyzed for Metoclopramide concentration. Blood samples were collected for hematology, coagulation, and clinical chemistry tests from each animal during Weeks -1, 4, and 13 and from recovery animals during Week 18. During Week 14, four animals/sex/group were anesthetized, weighed, exsanguinated, and necropsied. At necropsy, macroscopic observations were recorded, selected organs were weighed, and selected tissues were collected and preserved. For the recovery animals in Groups 1 and 4, this was done during Week 18. Microscopic examinations were done on selected tissues, including four sections of nasal turbinates, from each animal.

All animals survived to the respective scheduled sacrifice. There were no test material-related clinical observations noted. There were no test material-related effects on body weights, body weight changes, food consumption, or ophthalmic observations. No test material-related nasal irritation observations were noted except one male and one female given 240 mg/animal/day had very slight discharge during the study; these observations were not considered adverse.

Noncompartmental analysis was applied to the individual plasma Metoclopramide concentration data for males and females at each dose level. Maximum plasma concentration (C_{max}) following the administration of the fourth dose of the day and its corresponding time to maximum concentration (T_{max}) were determined. After the fourth intranasal administration of the day, Metoclopramide rapidly appeared in plasma and reached its maximum concentration within 10 to 30 minutes of dosing. Females had slightly higher C_{max} values than males on all 3 collection days. The mean C_{max} values increased in approximate proportion to the increase in the dose. The mean C_{max} values on Days 30 and 92 were generally similar to those observed on Day 1, indicating no accumulation of the test material in the rabbits after 13 weeks of dosing.

Administration of Metoclopramide had no obvious effects on clinical pathology test results. Of uncertain relationship to administration of the test material were mildly lower red blood cell count, hemoglobin, hematocrit, total protein, albumin, calcium, and triglycerides for males given 240 mg/animal/day. These small differences were not observed for females given 240 mg/animal/day and were absent in the treated males after the 4-week recovery. These differences were not associated with correlative clinical observations or anatomic pathology findings and were not considered adverse.

The intranasal installation of Metoclopramide Nasal Spray did not cause any biologically important changes in the anatomic pathology data. There were no test material-related effects on organ weights, or on macroscopic or microscopic findings.

Based on the results of this study, daily administration of Metoclopramide Nasal Spray by intranasal installation, four times/day for at least 13 weeks, to male and female Hra:(NZW)SPF rabbits is well-tolerated; Metoclopramide does not accumulate in rabbits; and it produced no observable adverse effects at doses up to and including 240 mg/animal/day.

PURPOSE

The purpose of this study was to assess the toxicity and to determine the bioavailability of Metoclopramide Nasal Spray when administered as an intranasal spray to rabbits for at least 13 weeks and to assess the reversibility of any effects after a 4-week recovery period.

REGULATORY COMPLIANCE

All aspects of this study were in accordance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations, Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments.

TEST AND CONTROL MATERIALS

Test Material

The test material, Metoclopramide Nasal Spray, 6 mL/bottle (200 mg/mL), Lot No. R98 0104, is a clear liquid. It was received at Covance on

The test material was stored at room temperature, protected from light.

Information on synthesis methods, stability, purity, composition, or other characteristics that define the test material is the responsibility of, or is on file with, the Sponsor.

Control Material

The control material, 0.9% Sodium Chloride for Injection, USP [saline (Roberts Pharmaceutical Canada Inc., Oakville, Ontario, Canada)], 20 mL vials, Lot No. 46-165-DK (expiration date:), is a clear liquid. It was received at Covance on

The control material was stored at room temperature.

Information on synthesis methods, composition, or other characteristics that define the control material is on file with the manufacturer.